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Full Paper

Nitrosonium-Mediated Phenol–Arene Cross-Coupling Involving Direct C–H Activation

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The nitrosonium ion (NO^+) is a highly versatile nitration and nitrosation reagent, as well as a strong one-electron oxidant. Herein, we describe an environmentally benign and mild method for the in situ formation of NO^+ from readily available inorganic nitrate salts, i.e. lithium nitrate, through a finely tuned interplay between formic acid and MeOH, which are used as the solvent system. This methodology was applied to the NO^+-induced oxidative C–H activation of methoxy-substituted phenols, which are versatile lignin-derived aromatic feedstocks, to achieve C–C cross-coupling reactions with arenes. The regeneration of NO^+ by atmospheric molecular oxygen enables substoichiometric use of the nitrate.

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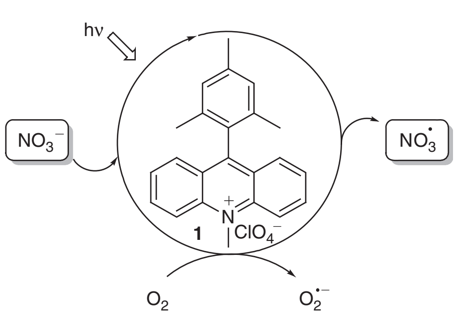
Introduction

Lignin is a complex amorphous biopolymer and a major component of natural woods. Its unique structure that comprises different methoxylated phenylpropane units makes lignin a viable, abundant natural resource for the sustainable production of aromatic compounds. For example, the catalytic depolymerization of lignin typically provides a mixture of substituted phenols, for example guaiacol and syringol derivatives.[1] In light of the continuing decline of fossil fuel resources the development of synthetic methods that enable transformation and functionalization of lignin-derived phenolic and oxygenated aromatics is becoming an increasingly important area of research.

The research group of one of us has a long-standing interest in exploring the application of the highly reactive nitrate radicals, $NO_3^\bullet$, as both oxygen atom donor and as one-electron oxidant (E ($NO_3^\bullet/NO_3^-$) = 2.0 V versus standard calomel electrode (SCE) in acetonitrile (MeCN)) in synthetic organic chemistry.[2,3] However, a major limitation has been the somewhat laborious methods for their generation, such as electrochemical anodic oxidation of inorganic nitrate salts,[4] reaction of nitrogen dioxide with ozone,[5] or photolysis of ceric ammonium nitrate (CAN) with UV light ($\lambda = 350$ nm).[2,6] We therefore recently initiated a research program to explore $NO_3^\bullet$ generation through oxidation of inorganic nitrates using visible light photoredox catalysis. In the presence of the organic dye 9-mesityl-10-methylacridinium perchlorate (Acr^+-Mes, **1**)[7] and oxygen in air as terminal oxidant, $NO_3^\bullet$ could be produced (Scheme 1) and successfully applied to the oxidation of alkynes and aliphatic alcohols.[7a]

We wanted to extend this methodology to the $NO_3^\bullet$-induced oxidation of aromatic compounds. In fact, comparative mechanistic studies in the gas phase revealed that oxidation of phenols by $NO_3^\bullet$ should proceed with significantly higher rates than with non-hydroxylated arenes (rate constant for 2-methoxy-4-methylphenol (**1a**): $k = 8.41 \times 10^{-11}$ cm^3 molecule^{-1} s^{-1} and for 1,2-dimethoxybenzene: $k = 9.80 \times 10^{-15}$ cm^3 molecule^{-1} s^{-1} at 21°C in the gas phase).[8] The reaction with phenols is assumed to involve formation of a phenoxyl radical, either through direct hydrogen abstraction or through oxidative electron transfer, followed by deprotonation (the mechanism is shown in Scheme S1 in the Supplementary Material).[8,9] Phenoxyl radicals are important intermediates in the electrochemical,[10] and iron-catalyzed[11] C–C cross-coupling with electron-rich arenes by direct C–H activation. Thus, the different reactivity of $NO_3^\bullet$ towards phenols and arenes would provide a unique possibility for selective activation and cross-coupling, avoiding side reactions like homocoupling of the electron-rich arene coupling partner.[12] In particular, application of photocatalytically generated $NO_3^\bullet$ for the selective C–H



Scheme 1. Formation of $NO_3^\bullet$ by photooxidative activation of NO_3^- using Acr^+-Mes **1** as organic photocatalyst and air as terminal oxidant.[7a]

activation of phenols and subsequent C–C cross-coupling with arenes,[13] would represent a mild, metal-free, and operationally simple alternative approach to conventional cross-coupling strategies for aromatic compounds.

In this paper we report on the findings of this study, which has led to the serendipitous discovery of a novel methodology to generate nitrosonium ions (NO^+) from lithium nitrate ($LiNO_3$) that can be used to achieve unsymmetrical aromatic cross-coupling reactions.

Results and Discussion

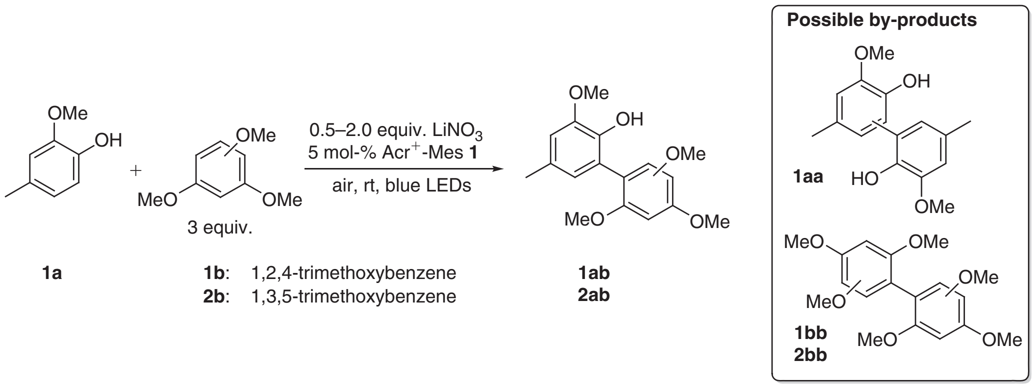
For the initial investigations the optimized conditions for the $NO_3^{\bullet}$-mediated oxidation of aliphatic alcohols were applied (5 mol-% Acr^+-Mes **1** and 0.5–2.0 equiv. $LiNO_3$ in MeCN open to air at room temperature).[7a] 2-Methoxy-4-methylphenol (**1a**) was used as a model phenolic compound (E_{ox} (**1a**) = 1.10 V versus SCE in MeCN),[14] which was treated with 3 equivalents of 1,2,4-trimethoxybenzene (**1b**) or 1,3,5-trimethoxybenzene (**2b**). The product distribution was qualitatively analyzed by gas chromatography–mass spectrometry (GC-MS). The results are compiled in Table 1.

Interestingly, although MeCN has been frequently used as a solvent for reactions involving $NO_3^{\bullet}$,[3,5b,6,7a] almost no conversion of the starting materials and only trace amounts of the homocoupling product (**1aa**) could be detected, which was identified by the [M^+] signal at *m/z* 274.1 (entries 1, 2). Using silver nitrate ($AgNO_3$) as a source of nitrate ions did not improve the outcome (entry 3). Prolonged reaction times led to formation of traces of the desired cross-coupling products **ab** as a mixture of isomers, which was confirmed by the [M^+] signal in the GC-MS at *m/z* 304.1 for **1ab** and **2ab** (entries 3, 4). It is worth noting that arene homocoupling products **1bb** or **2bb** were not detected under these conditions.

A possible explanation for the low product formation is the high reactivity and limited lifetime of the putative intermediately formed phenoxyl radical. In order to increase its lifetime we explored the reaction using the fluorinated alcohol 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as solvent, which is known to stabilise electrophilic radical intermediates and to enable selective reaction with the most nucleophilic species present in the reaction mixture.[15] Unfortunately, performing the reaction in a mixture of HFIP/MeOH (8 : 2) did not improve either the yield or selectivity of the reaction (entries 5, 6).

We next explored a 9 : 1 mixture of formic acid and methanol as a solvent system, which has been shown in electrochemical studies on phenol–arene C–C cross-coupling reactions to provide similar solvent properties and stabilising effects as fluorinated alcohols, albeit with slightly reduced yields.[16] To our delight, under these conditions formation of the desired cross-coupling products **1ab** and **2ab** clearly occurred, which was confirmed by the [M^+] signal in the GC-MS at *m/z* 304.1 for both products. Thus, the reaction between the methoxyphenol **1a** and arene **1b** provided the cross-coupling product **1ab** as a 1 : 10 mixture of isomers (entry 7). In addition a minor signal at *m/z* 334.1 was observed, which could be assigned to the homocoupling product **1bb**. The reaction involving trimethoxybenzene **2b** gave also two cross-coupling products **2ab**, with a remarkable selectivity (1 : 50) for one isomer (entry 8). The corresponding homocoupling product **2bb** could not be detected, which is most likely due to a higher steric hindrance of the arene **2b** compared with **1b** and its less favourable oxidation potential, i.e. E_{ox} (**1b**) = 1.01 V versus SCE and E_{ox} (**2b**) = 1.34 V versus SCE in MeCN.[14] Interestingly, both reaction time and equivalents of the

Table 1. Phenol–arene cross-coupling: Screening of experimental conditions



Entry	Arene	Solvent	Equiv. $LiNO_3$	Time [h]	Products
1	**1b**	MeCN	0.5	4	**1aa** (traces)
2	**1b**	MeCN	2	4	**1aa** (traces)
3	**1b**	MeCN	2^A	18	**1aa** (traces, 1 isomer) ≈ **1ab** (traces, 2 isomers)
4	**2b**	MeCN	2	22	**1aa** (traces, 2 isomers, 1 : 1) ≈ **2ab** (traces, 2 isomers, 1 : 10)
5	**1b**	HFIP/MeOH (8 : 2)	2	17	**1aa** (traces, 1 isomer) < **1ab** (traces, 2 isomers, 1 : 10)
6	**2b**	HFIP/MeOH (8 : 2)	2	20	**1aa** (traces, 1 isomer) < **2ab** (traces, 2 isomers, 1 : 1)
7	**1b**	formic acid/MeOH (9 : 1)	2	17	**1ab** (2 isomers, 1 : 10) > **1bb** (1 isomer)
8	**2b**	formic acid/MeOH (9 : 1)	2	20	**2ab** (2 isomers, 1 : 50)
9	**1b**	formic acid/MeOH (9 : 1)	1	4	**1ab** (2 isomers, 1 : 10) > **1bb** (1 isomer)
10	**1b**	formic acid/MeOH (9 : 1)	–	4	**1ab** (traces, 2 isomers, 1 : 5) > **1bb** (traces)

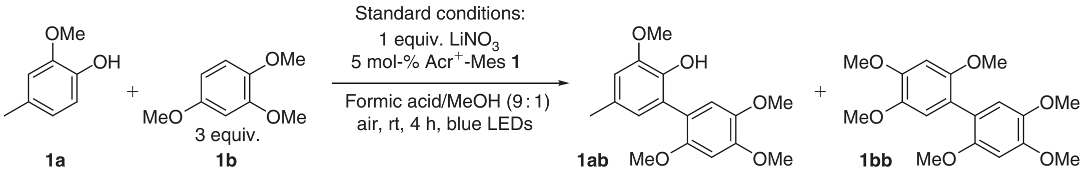
[A] $AgNO_3$ was used instead of $LiNO_3$.

nitrate salt could be reduced without dramatically decreasing the conversion of the reactants (entry 9). On the other hand, in the absence of $LiNO_3$ the coupling products **1ab** and **1bb** were only detected in trace amounts (entry 10) confirming that nitrate is essential for the reaction.

After this initial qualitative screening, we performed a series of quantitative control experiments for the reaction of **1a** with **1b** to validate the photocatalytic nature of the reaction.[13] Yields were determined by GC using 2-methylnaphthalene as an internal standard, which was calibrated against authentic samples of **1ab** and **1bb** (see Supplementary Material). The results are compiled in Table 2. To our surprise, the cross-coupling product **1ab** could be obtained in comparable yields without either Acr^+-Mes **1** or blue light irradiation (entries 2, 5, 8). This clearly indicates that the reaction was not photocatalytic and that the role of the nitrate salt required reconsideration, since formation of $NO_3^\bullet$ without the photocatalyst system should not be possible.[7a] In addition, we also found a strong dependence between the reaction outcome and the order of addition of the reactants, in particular with regards to the timing of the MeOH addition to the mixture of $LiNO_3$ and formic acid (the phenol **1a** and arene **1b** were always added last; entries 1–3, 4–6, or 7–9). We noticed that: (i) treatment of $LiNO_3$ with formic acid led, after an induction period of ~10 s, to a colour change to faint blue that is characteristic for N_2O_3,[17] and which disappeared after 1 s with evolution of a colourless gas (CO_2); (ii) after additional 5–10 s a brown gas ($NO_2^\bullet$) evolved; (iii) the highest yields of cross-coupling products were observed when MeOH was added at the starting point of $NO_2^\bullet$ evolution (reaction conditions **B**). When MeOH was added before the gas evolution occurred (reaction conditions **A**) or delayed after 10–15 s of brown gas evolution (reaction conditions **C**) the yields decreased. This can be rationalised by the low solubility of $NO_2^\bullet$ in pure formic acid, which led to $NO_2^\bullet$ loss through degassing. Addition of MeOH to the reaction mixture prevented degassing and enabled cross-coupling. (iv) Changing the order of solvent addition, i.e. first MeOH, second formic acid, yielded almost no conversion. Obviously, highly acidic conditions are required in the initial stage of the reaction, which is provided by formic acid. Overall these findings are a clear indication for in situ formation of a catalytically active species.

Based on these findings and literature data on the reactions between nitric and formic acid,[17,18] we propose that the nitrosonium cation (NO^+) is the key-species formed in our reaction system, which acts as a substoichiometric oxidant and initiates oxidation of aromatic compounds ($E\,(NO^+/NO^\bullet) = 1.27$ V versus SCE in MeCN).[19] In Scheme 2 is shown the proposed mechanistic rationale for the in situ formation of NO^+. Under the acidic conditions of the reaction system, partial protonation of nitrate leads to nitric acid (Eqn 1). The latter is known to be reduced to nitrous acid (HNO_2) by formic acid, with release of carbon dioxide (CO_2) as by-product (Eqn 2). Nitrous acid is in equilibrium with its anhydride (N_2O_3) (Eqn 3), which

Table 2. Influence of the time delay between the addition of formic acid and MeOH



Entry	Variation from standard conditions[A]	MeOH addition[B]	Conv. **1a**[C] [%]	Yield **1ab**[C, D] [%]	Selectivity **ab**[D] : **bb**
1	–	**A**	2	0	–
2	–	**B**	91	86[E]	7 : 1
3	–	**C**	12	14	4 : 1
4	without light	**A**	1	0	–
5	without light	**B**	90	63[E]	7 : 1
6	without light	**C**	50	47	17 : 1
7	without Acr^+-Mes	**A**	–	1	–
8	without Acr^+-Mes	**B**	77	74	7 : 1
9	without Acr^+-Mes	**C**	3	6	6 : 1
10	without light/without Acr^+-Mes 0.5 equiv. $LiNO_3$	**B**	93	78[E]	7 : 1
11	without light/without Acr^+-Mes 0.25 equiv. $LiNO_3$	**B**	27	28	6 : 1
12	without light/without Acr^+-Mes formic acid/MeOH (1 : 9) 0.5 equiv. $LiNO_3$	**B**	12[F]	traces	–
13	without light/without Acr^+-Mes formic acid/MeOH (1 : 1) 0.5 equiv. $LiNO_3$	**B**	91	21[E]	38 : 1

[A] Order of addition: 1) $LiNO_3$, and if mentioned photocatalyst Acr^+-Mes **1**, 2) formic acid, 3) MeOH, 4) 1,2,4-trimethoxybenzene **1b**, 5) 2-methoxy-4-methylphenol **1a**.

[B] **A**: before bubbling occurs; **B**: at the starting point of brown gas evolution; **C**: after 10–15 s of brown gas evolution.

[C] Conversion and yields were determined by GC using 2-methylnaphthalene as the internal standard.

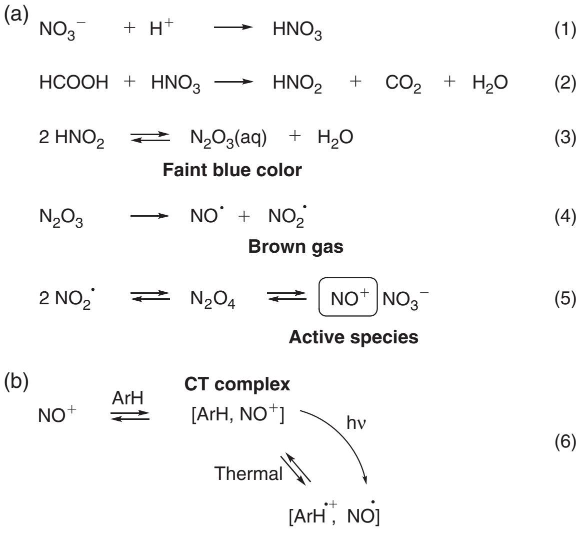
[D] Main isomer.

[E] Overoxidation to yield a teraryl product was observed ($[M^+]$ at *m/z* 470.2).

[F] Formation of the homocoupling product **1aa** was observed, the mass peak of **1bb** was not detected.

dissociates at room temperature into nitric oxide ($NO^{\bullet}$) and nitrogen dioxide ($NO_2^{\bullet}$) (Eqn 4). $NO_2^{\bullet}$ is in equilibrium with its dimer dinitrogen tetroxide (N_2O_4), which dissociates ionically to $NO^+NO_3^-$ in the polar and acidic solvent system (Eqn 5).[18] NO_3^- re-enters the reaction system through Eqn 1. An alternative formation mechanism, which considers the direct formation of NO^+ from HNO_2 is given in the Supplementary Material.[18]

The NO^+-mediated oxidation of arenes involves intermediate formation of a charge transfer (CT) complex between NO^+ and the arene.[19c,20] The actual electron transfer could principally occur either through a thermal equilibrium reaction, or photochemically (Eqn 6, for a detailed mechanism see the Supplementary Material). A comparison of the reaction outcome (using method **B**) under photocatalytic (entry 2), photochemical (entry 8), and photocatalyst-free conditions in the absence of light (entry 10) indicated a thermal and not a photochemical process.

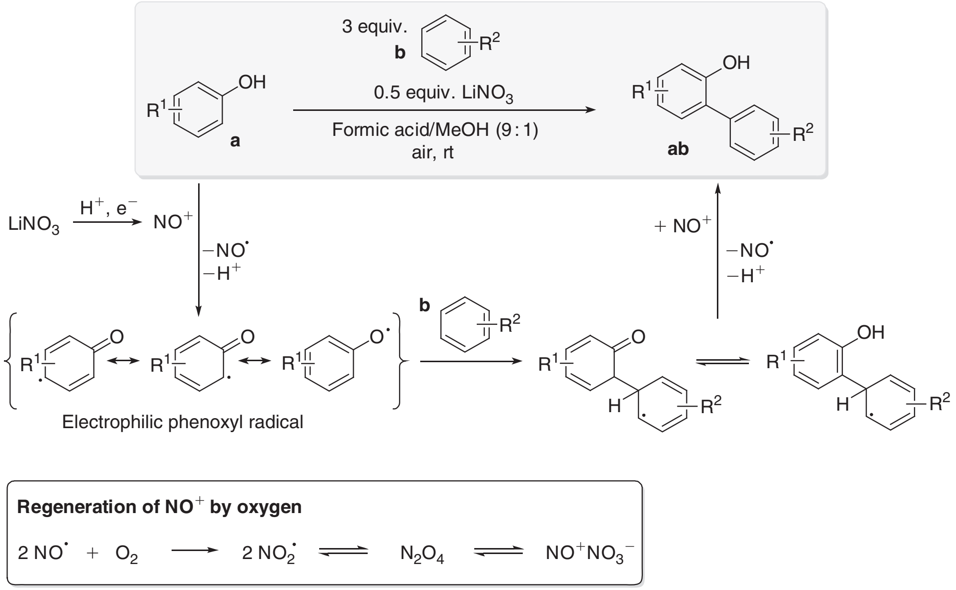


Scheme 2. Proposed in situ generation of the active NO^+ species (a) and mechanism of the NO^+-mediated oxidation of aromatic compounds (b).[18,19c,20]

Interestingly, only few examples are known for NO^+-mediated dehydrogenative arene coupling reactions, which are limited to the homocoupling of activated arenes[19b,21] and to intramolecular coupling reactions.[22] As NO^+ sources, $NO^+BF_4^-$ or other NO^+ precursors in combination with strong acids ($NaNO_2/CF_3SO_3H$ or $NO_2^{\bullet}/CF_3COOH$) were applied. The access to NO^+ from readily available non-toxic nitrate salts through a finely tuned interplay between formic acid and MeOH discovered in this study could provide a mild and attractive alternative approach to this synthetically versatile intermediate avoiding the use of carcinogenic $NaNO_2$ and toxic $NO_2^{\bullet}$ gas in combination with harsh acid conditions.[23]

In fact, reduction of the amount of $LiNO_3$ from 1.0 to 0.5 equiv. provides the product in comparable yields (Table 2, entry 10). This shows that NO^+ is regenerated under the applied conditions and can be used substoichiometrically. A further decrease to 0.25 equiv. of $LiNO_3$ led to reduced conversion and yield (entry 11). Variations of the ratio of formic acid to MeOH had a significant impact on the conversion and product distribution (entries 12, 13). By applying formic acid/MeOH (1 : 9), low conversion of the starting material **1a** was observed. In contrast, a 1 : 1 formic acid/MeOH mixture resulted in an increased over-oxidation to produce a teraryl adduct consisting of one phenol and two arene moieties (not shown), which was identified by its molecular ion at *m/z* 470.2. Best results were obtained for 0.5 equiv. of $LiNO_3$ in a formic acid/MeOH mixture of 9 : 1 and an excess of the arene coupling partner **1b** of 3 equiv. (entry 10).

Although various radical and ionic nitrogen oxides are formed as intermediates in this reaction, which could principally also lead to aromatic nitration[19c,20b,21b,24] and nitrosation[19c,20c] products, the mass balance for the phenolic compound **1a** under most conditions showed a relatively clean conversion into the aforementioned products (Table 2).[25] In contrast to this, the mass balance for 1,2,4-trimethoxybenzene **1b** suggests the occurrence of side reactions. In fact, we observed colour changes upon addition of the aromatic components to the formic acid/MeOH/$LiNO_3$ mixture (method **B**).



Scheme 3. Proposed mechanism for the NO^+-mediated phenol–arene cross-dehydrogenative coupling.[27]

This could be due to nitrosation as a minor pathway,[26] but no products could be isolated or detected. The observed colour changes could also result from the formation of CT complexes between NO^+ and the aromatic components.[20b] The nitration of the starting materials **1a** ($[M^+]$ signal in the GC-MS at *m*/*z* 183.1) and **1b** ($[M^+]$ signal in the GC-MS at *m*/*z* 213.1) could be detected in traces for the MeOH addition method **B**, method **A** showed no nitration, and for method **C** trace amounts of nitration could be observed in some cases. The amount of nitration products correlates with the product formation **1ab**.

Based on these results, we propose the following mechanism for the NO^+-induced phenol–arene C–C cross-coupling (Scheme 3): NO^+ is formed in situ from the nitrate salt by treatment with formic acid and MeOH according to Scheme 2.[18] NO^+ oxidizes the phenol component **a**, which undergoes deprotonation to give an electrophilic phenoxyl radical that is trapped by the electron-rich arene nucleophile **b**.[27] The final C–C cross-coupling product **ab** is formed after a second oxidation/deprotonation step. The two equivalents of $NO^\bullet$ formed in this sequence are re-oxidized by oxygen in air to $NO_2^\bullet$,[18a,21] which is in equilibrium with the dimer N_2O_4 or $NO^+NO_3^-$.[18a,e] However, further experiments are required to provide more detailed insight into the mechanism, for example by using NO^+ scavengers (e.g. azides) and variation of the NO^+ source.

Conclusion

In conclusion, an environmentally friendly and mild protocol for the in situ formation of highly oxidizing NO^+ could be developed. The nitrosonium cation NO^+ can be conveniently generated from readily available nitrate salts by a combination of formic acid and MeOH as solvent system. Apart from its role as acid, the reducing properties of formic acid are decisive for the generation of NO^+. Methanol as co-solvent is essential to prevent degassing of $NO_2^\bullet$, which is formed as an intermediate and constitutes a precursor for NO^+. The method was applied to the NO^+-induced oxidative phenol–arene C–C cross-coupling of typical lignin-derived platform chemicals. Regeneration of the oxidant by air enables the substoichiometric use of NO^+ or the corresponding nitrate source, respectively.

Experimental

General Information and Materials

Commercial reagents and starting materials were purchased and used without further purification. NMR spectra were recorded on a Varian INOVA 400 (^{1}H at 400 MHz and ^{13}C at 100 MHz). Cyclic voltammetry (CV) measurements were conducted with a three-electrode potentiostat galvanostat PGSTAT302N from Metrohm Autolab. A glassy carbon working electrode, a platinum counter electrode, and a silver wire as reference electrode were used. Potentials were converted into SCE reference values according to Pavlishchuk and Addison.[28] Photocatalytic reactions were performed with blue light emitting diodes (LEDs) (Osram Oslon SSL 80, $\lambda_{Peak} = 440$ nm, royal blue, operated at 700 mA).

Quantitative GC-MS Investigations (Table 2)

GC-MS measurements were performed on a 7890A GC system from Agilent Technologies with an Agilent 5975 MSD Detector. Data acquisition and evaluation was done with an MSD ChemStation E.02.02.1431. The GC-MS oven temperature program was adjusted as follows: an initial temperature of 70°C was maintained for 5 min, the temperature was then increased at a rate of 10°C min^{-1} over a period of 18 min until the final temperature (250°C) was reached and maintained for 17 min. A calibration was performed using the internal standard method (multi-level calibration, internal standard: 2-methylnaphthalene). Authentic samples of each compound were used for calibration.

General Procedure

In a snap vial equipped with a magnetic stirring bar the respective amount of $LiNO_3$ and 5 mol-% Acr^+-Mes **1** (if mentioned) were dissolved in 1 mL of the formic acid/MeOH mixture (method of MeOH addition and ratio as indicated). The arene **1b** (3.0 equiv., 0.70 mmol) and phenol component **1a** (1.0 equiv., 0.23 mmol) were added successively and the resulting mixture was stirred at room temperature open to air for the indicated time. If mentioned the sample was irradiated through the vial's plane bottom side with blue LEDs. After the addition of the internal standard, the sample was filtered over a small plug of silica gel. The plug was rinsed with MeOH (1 : 1), diluted, and submitted to GC-MS.

Supplementary Material

Experimental details, cyclic voltammetry data, and a detailed mechanism of the $NO_3^\bullet$-induced oxidation of phenols and the NO^+-mediated arene oxidation as well as an alternative pathway for the in situ NO^+ formation and regeneration are available on the Journal's website.

Acknowledgements

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[26] Gowenlock et al. observed an intense green colour upon treatment of 1,3-dimethoxybenzene **3b** with the equilibrium mixture $NO_2^{\bullet}/N_2O_4$ in dichloromethane. The colour was assigned to a nitrosation reaction and subsequent oxidation: B. G. Gowenlock, B. King, J. Pfab, *J. Chem. Res.* **2000**, *2000*, 276. Treatment of **3b** with formic acid/MeOH (9 : 1), $LiNO_3$ (0.5 equiv.) (method **B**) results in an intense emerald green colour, which implies the formation of traces of nitrosation products and gives indirect evidence to the formation of $NO_2^{\bullet}/N_2O_4$ and the ionic $NO^+NO_3^-$.

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